

We Claim:

1. A composition comprising an association complex of a polyacid (PA) and a polyalkylene oxide (PO), which is hemostatic and possesses at least one additional  
5 property selected from the group consisting of antiadhesion, bioadhesiveness, antithrombogenicity and bioresorbability, and wherein the pH of said composition is below about 7.5.

2. The composition of claim 1, wherein said polyacid is selected from the group  
10 consisting of a carboxypolysaccharide, polyacrylic acid, polyamino acid, polylactic acid, polyglycolic acid, polymethacrylic acid, polyterephthalic acid, polyhydroxybutyric acid, polyphosphoric acid, polystyrenesulfonic acid, and copolymers of said polyacids.

3. The composition of claim 1, wherein the polyacid is a carboxypolysaccharide  
15 selected from the group consisting of carboxymethyl cellulose (CMC), carboxyethyl cellulose, chitin, carboxymethyl chitin, hyaluronic acid, alginate, propylene glycol alginate, pectin, carboxymethyl dextran, carboxymethyl chitosan, heparin, heparin sulfate, chondroitin sulfate and polyuronic acids including polymannuronic acid, polyglucuronic acid and polyguluronic acid..

4. The composition of claim 1, wherein the polyacid is carboxymethylcellulose.

5. The composition of claim 1, wherein the polyacid is carboxymethylcellulose  
25 having a molecular weight in the range of about 10 kd to about 10,000 kd and a degree of substitution in the range of greater than about 0 to about 3.

6. The composition of claim 1, wherein said polyalkylene oxide is selected from the  
30 group consisting of polypropylene oxide, polyethylene glycol, polyethylene oxide, and PEO/PPO block copolymers.



17. The composition of claim 16, wherein said cation is selected from the group consisting of  $\text{Fe}^{+3}$ ,  $\text{Al}^{+3}$ , and  $\text{Cr}^{+3}$ .

18. The composition of claim 1, further comprising a divalent cation.

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19. The composition of claim 18, wherein said cation is a divalent cation selected from the group consisting of  $\text{Ca}^{+2}$ ,  $\text{Zn}^{+2}$ ,  $\text{Mg}^{+2}$  and  $\text{Mn}^{+2}$ .

20. The composition of claim 1, wherein the pH of the gel is in the range of about 2.0 to about 7.5.

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21. The composition of claim 1, wherein the pH of the gel is in the range of about 2.5 to about 6.0.

22. The composition of claim 1, further comprising a drug.

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23. The composition of claim 1, further comprising a drug selected from the group consisting of antithrombogenic drugs, hemostatic agents, anti-inflammatory drugs, hormones, chemotactic factors, analgesics, growth factors, cytokines, osteogenic factors and anesthetics.

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24. The composition of claim 1, further comprising a drug selected from the group consisting of heparin, tissue plasminogen activator, thrombin, aspirin, ibuprofen, ketoprofen, proteins and peptides containing an RGD motif, and non-steroidal anti-inflammatory drugs.

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25. The composition of claim 1 having a viscosity below about 500,000 centipoise.

26. The composition of claim 1, wherein said composition is dried to form a membrane.

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35. The method of claim 27, further comprising the step of sterilizing the composition.

36. A method for providing hemostasis comprising the step of placing the composition of claim 1 in contact with a bleeding tissue.

37. A method for providing hemostasis comprising the steps of:

- (a) accessing a surgical site;
- (b) performing a surgical procedure; and
- (c) placing the composition of claim 1 in contact with a bleeding tissue.

38. The method of claim 37, wherein said surgical procedure is selected from the group consisting of abdominal, ophthalmic, orthopedic, gastrointestinal, thoracic, cranial, cardiovascular, gynecological, urological, plastic, musculoskeletal, spinal, nerve, tendon, otorhinolaryngological and pelvic.

39. The method of claim 37, wherein said surgical procedure is selected from the group consisting of appendectomy, cholecystectomy, hernial repair, lysis of peritoneal adhesions, kidney surgery, bladder surgery, urethral surgery, prostate surgery, salpingostomy, salpingolysis, ovariolysis, removal of endometriosis, surgery to treat ectopic pregnancy, myomectomy of uterus, myomectomy of fundus, hysterectomy, laminectomy, discectomy, tendon surgery, spinal fusion, joint replacement, joint repair, strabismus surgery, glaucoma filtering surgery, lacrimal drainage surgery, sinus surgery, ear surgery, bypass anastomosis, heart valve replacement, thoracotomy, synovectomy, chondroplasty, removal of loose bodies and resection of scar tissue.

40. The method of claim 37, wherein said step of accessing is carried out using an arthroscope.

41. A method for decreasing post-traumatic bleeding, comprising the step of delivering to a site of trauma the composition of claim 1.

42. The method of claim 41, further comprising, prior to the step of delivering, the step of accessing a site of trauma.

43. A method for decreasing bleeding caused by a surgical instrument, comprising coating said surgical instrument with the composition of claim 1 prior to using said surgical instrument.

44. A dried hemostatic membrane comprising a composition of claim 1.

45. The dried hemostatic membrane of claim 44, which possesses at least one additional property selected from the group consisting of bioresorbability, bioadhesiveness, antithrombogenicity, and antiadhesion, and wherein the composition has a pH in the range of about 2.5 to about 7.5 and is hydratable by at least about 100%.

46. The membrane of claim 44, wherein the PA is a CPS selected from the group consisting of carboxymethyl cellulose (CMC), carboxyethyl cellulose, chitin, carboxymethyl chitin, hyaluronic acid, alginate, propylene glycol alginate, carboxymethyl chitosan, pectin, carboxymethyl dextran, heparin, heparin sulfate, chondroitin sulfate and polyuronic acids including polymannuronic acid, polyglucuronic acid and polyguluronic acid.

47. The composition of claim 44, wherein the molecular weight of the CPS is between 10 kd and 10,000 kd.

48. The composition of claim 44, wherein said PO is a PE having a molecular weight between about 200d and about 8000 kd.

49. The composition of claim 44, wherein the CPS is CMC.

50. The composition of claim 48, wherein the PE is polyethylene oxide (PEO).

5 51. The composition of claim 44, wherein the proportion of total solids content of the CPS is from 10 % to 99 % by weight, and the proportion of the PE is from 1 % to 90 % by weight.

52. The composition of claim 44, wherein the degree of substitution of the CPS is  
10 from greater than about 0 up to and including about 3.

53. The composition of claim 44 further comprising a drug.

54. The composition of claim 53, wherein said drug is selected from the group  
15 consisting of antibiotics, hemostatic agents, anti-inflammatory agents, hormones, chemotactic factors, peptides and proteins containing an RGD motif, analgesics, and anesthetics.

55. The composition of claim 44, further comprising a plasticizer.  
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56. The composition of claim 55, wherein the plasticizer is selected from the group consisting of glycerol, ethanolamines, ethylene glycol, 1,2,6-hexanetriol, monoacetin, diacetin, triacetin, 1,5-pentanediol, PEG, propylene glycol, and trimethylol propane.

25 57. The composition of claim 55, wherein the concentration of said plasticizer is in the range of greater than about 0 % to about 30 % by weight.

58. The composition of claim 55, wherein the plasticizer is glycerol in a concentration in the range of about 2 % to 30 % by weight.  
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59. The composition of claim 44, wherein the adherence of platelets to the surface of said composition is in the range of about 0 platelets per 25,000  $\mu\text{m}^2$  to about 65 per 25,000  $\mu\text{m}^2$ .

5 60. The composition of claim 1, wherein the bleeding time is reduced from that of untreated tissues by at least 1/2.

61. The method of claim 27, further comprising the step of sterilizing the composition by autoclaving,  $\gamma$ -irradiation, filtration, or exposure to ethylene oxide.

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62. The method of claim 37, wherein said step of placing said composition is accomplished using an endoscope.

15 63. The composition of claim 1, wherein the pH of said composition is below about 5.0.

64. The composition of claim 1, wherein the pH of said composition is below about 4.0.

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65. The composition of claim 1, wherein the pH of said composition is below about 3.0.

25 66. A composition comprising an association complex of a polyacid (PA), a polyalkylene oxide (PO) and a multivalent cation, which is hemostatic and possesses at least one additional property selected from the group consisting of antiadhesion, bioadhesiveness, antithrombogenicity and bioresorbability, and wherein the pH of said composition is below about 7.5.



67. The composition of claim 66, wherein said multivalent cation is selected from the group consisting of  $\text{Ca}^{2+}$ ,  $\text{Mg}^{2+}$ ,  $\text{Mn}^{2+}$ ,  $\text{Fe}^{3+}$ ,  $\text{Cr}^{3+}$ ,  $\text{Zn}^{2+}$  and  $\text{Al}^{3+}$ .

68. The composition of claim 66, wherein said multivalent cation is  $\text{Ca}^{2+}$ .

69. A method for manufacturing a hemostatic composition, comprising the steps of:

- (a) selecting a polyacid;
- (b) selecting a polyalkylene oxide;
- (c) forming a solution of said polyacid and said polyalkylene oxide;
- (d) adding a multivalent cation; and
- (e) adjusting the pH of said composition to the range of below about 7.5.

70. The method of claim 69, wherein said multivalent cation is selected from the group consisting of  $\text{Ca}^{2+}$ ,  $\text{Mg}^{2+}$ ,  $\text{Mn}^{2+}$ ,  $\text{Fe}^{3+}$ ,  $\text{Cr}^{3+}$ ,  $\text{Zn}^{2+}$  and  $\text{Al}^{3+}$ .

71. The method of claim 69, wherein said multivalent cation is  $\text{Ca}^{2+}$ .

72. The composition of claim 1, further comprising thrombin.

73. The composition of claim 1, wherein said polyalkylene oxide is polyethylene glycol having a molecular weight in the range of about 1000 Daltons to about 40,000 Daltons.

74. The composition of claim 1, wherein said polyalkylene oxide is polyethylene glycol having a molecular weight in the range of about 1000 Daltons to about 20,000 Daltons.

75. The composition of claim 44, wherein the molecular weight of the CPS is between about 10 kd and 1000 kd.

76. The composition of claim 1, further comprising thrombin.

77. The composition of claim 1, further comprising a vasoconstrictor.

5 78. The composition of claim 77, wherein said vasoconstrictor is an adrenergic agonist.

10 79. The composition of claim 78, wherein said adrenergic agonist is selected from the group consisting of norepinephrine, epinephrine, phenylpropanolamine, dopamine, metaraminol, methoxamine, ephedrine, and propylhexedrine.

15 80. The composition of claim 1, further comprising fibrillar collagen.